REMARKS

Applicants request that the title of the invention be properly recorded in the USPTO's records. Specifically, change "ana" to --DNA-- and change "Method" to --Methods--. These changes were requested in a facsimile letter dated April 13, 2004 addressed to the Office of Initial Patent Examination's Filing Receipt Corrections, but a corrected filing receipt was not issued. Applicants have attached hereto a copy of the April 13, 2004 facsimile for Request of Filing Receipt.

Applicants further request that a corrected Notice of Recordation of Assignment Document be issued to delete the New England Biolabs, Inc. as the Assignee on Reel/Frame: 012921/0098 and to properly record the Assignment from William E. Jack and Andrew Gardner to New England Biolabs, Inc. Applicants have enclosed a copy of the Notice of Recordation of Assignment Document as well as the New England Biolabs, Inc. Recordation Form and Assignment which were not recorded.

Claim Rejections 35 USC §112 Second Paragraph

Claims 6, 8-11, 13, 18 and 23-26 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner asserts that claims 23-26 are indefinite in that there is no antecedent basis for ROX-acyclo-CTP.

Applicants have amended claim 23 to depend from claim 19. Claims 24-26 have similarly been amended to depend from claim 23. Applicants respectfully submit that the amendments overcome the Examiner's rejection.

The Examiner has rejected claims 6, 8-11, 13 and 18 as indefinite because the claims contain the trademark/trade name "BODIPY", "Vent", "Deep Vent", "9°N". Applicants have amended claim 6 by replacing the trademarked names of "BODIPY" with the actual names. "Vent", "Deep Vent" and "9°N" are not only trademarks, they are the names given to the particular products. Applicants have removed the "®" from the claims. Alternatively, if the above amendment does not overcome the rejection, Applicants could amend the claims to recite that these DNA polymerases are from particular organisms. Applicants respectfully submit that the amendments overcome Examiner's rejection.

Claim Rejections 35 U.S.C. §112 First Paragraph

The Examiner has rejected claims 1-7, 11, 14-17 and 19-31 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the Application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that claims 1-7, 11, 14-17 and 19-31 are directed to all possible methods for site-

specific incorporation of derivatized dideoxynucleotides, acyclonucleotides or derivatized acyclonucleotides into DNA. Furthermore, the Examiner asserts that the specification only provides representative methods comprising the use of Vent and variants of Vent DNA polymerases. Applicants respectfully disagree.

Applicants have demonstrated in the specification that Family B DNA polymerases share conserved protein sequences in several regions. More particularly, the exonuclease and active site motifs are conserved among Family B DNA polymerases. The similarity in composition leads to similarity in structure and function (see p. 14-15 of the specification). Specifically, Applicants illustrate Table 3 the protein sequence similarity of the exemplified Family B DNA polymerases with other members of Family B DNA polymerases. In Table 3, Motif B is significantly conserved within the range of Family B polymerases. This is starkly opposed to the last of amino acid conservation to Taq and T7 DNA polymerases of Family A DNA polymerases.

Applicants not only describe and support the homology between Family B DNA polymerases, but also teach and describe the claimed method using four separate and distinct Family B DNA polymerases. Vent, Deep Vent, Pfu and 9°N are not variants of each other, but are all derived from different organisms. Table 1 shows that variants with analogous mutations from this family of polymerases have similar effects. Moreover, Applicants have also

demonstrated that the exemplified Family B DNA polymerases have the same or similar pattern of nucleotide incorporation, which is further evidence that the claimed class of Family B DNA polymerases possess similar function and structure. Table 3 illustrates the similarity of Region III of Family B DNA polymerases, all of which are suitable for use in the claimed method. See also Figure 3 which demonstrates that all four exemplified polymerases have the same pattern of incorporation. Given the description in the specification of significant homology in Family B DNA polymerases and examples of four different Family B DNA polymerases, it would be apparent to the person of ordinary skill in the art that at the time the application was filed, the Applicants were in possession of the claimed invention. Accordingly, Applicants respectfully assert the basis for the Examiner's rejection is overcome and request that this rejection be withdrawn.

The Examiner also rejected claims 1-12, 14-17 and 19-31 under 35 U.S.C. §112, first paragraph, taking the position that the specification does not reasonably provide enablement for any method for site-specific incorporation or derivatized dideoxynucleotides, acyclonucleotides or derivatized acyclonucleotides into DNA comprising reacting any archaeon Family B DNA Polymerase, a primed DNA template and nucleotide solution containing the referred to nucleotide to produce fragments of DNA with the referred to nucleotide covalently attached to the 3'-terminal residue. Applicants respectfully disagree.

As noted above, Family B DNA polymerases demonstrate significant protein sequence conservation. The homology between Family B polymerases exhibits significant structural and functional similarities in these motif regions. Specifically, Applicants provided examples of four Family B DNA polymerases as well as variants thereof, that can be used for site-specific incorporation of derivatized dideoxynucleotides. Moreover, in Table 3, Applicants have described the similarity in Region III of other Family B DNA polymerases. Accordingly, Applicants submit that the skilled artisan could readily use the described method with any Family B DNA polymerase for site-specific incorporation with a reasonable expectation of success. Accordingly, Applicants respectfully submit that Examiner's rejection is overcome and request that this rejection be withdrawn.

The Examiner also takes the position that claims 1-3 are so broad as to encompass any method for site-specific incorporation of derivatized dideoxynucleotides, acyclonucleotides or derivatized acyclonucleotides into DNA. Applicants respectfully disagree.

Applicants respectfully submit that Vent, Deep Vent, Pfu and 9°N are not isolated and limited examples of the claimed method. These Family B DNA polymerases are shown here as mere representatives of the Family B DNA polymerases. It is respectfully submitted for reasons noted above that Family B DNA polymerases many conserved motifs that would lead a person of ordinary art to expect that other polymerases in that family will behave similarly. In

other words, the exemplified polymerases are merely representative members of Family B polymerases, all of which have similar structure and function. It logically follows that Family B polymerases will have similar functions as the exemplified polymerases. Therefore, Applicants submit that the claimed method is not limited to the four enzymes and that the skilled artisan would expect the claimed method to be effective for other members of the Family B DNA polymerases. Applicants respectfully submit that Examiner's rejection is overcome and request that this rejection be withdrawn.

The Examiner also asserts that the specification does not establish: (A) regions of the protein structure which may be modified without effecting the specifically claimed DNA polymerases activity(s); (B) the general tolerance of archaeon Family B polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of an archaeon Family B DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Specifically, the Examiner asserts that Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the claimed

methods of use of any archaeon Family B DNA polymerase. Applicants respectfully disagree.

Applicants have demonstrated areas of significant homology between numerous members from Family B DNA polymerase (Table 3). In addition, Applicants have described starting materials and assays which may be used to determine modified nucleotide incorporation. Assays illustrated in Figures 1 and 6 and described in Example 1 illustrates the incorporation of the derivatized nucleotides using the exemplified Family B DNA polymerases in the claimed method. Applicants have further shown that Family B DNA polymerases can be modified with the exemplified approach and that the approach will also be successful when applied to other members of the Family B DNA polymerases.

While Applicants have claims directed to specific mutants claimed in claims 14-17, Applicants respectfully submit that the specification adequately describes and enables the scope of the claims. Specifically, in Tables 1 and 3, the regions of the protein which may be modified are identified. The assay and method for determining which modifications will work is described in Figures 1 and 6 and Example 1. Accordingly, Applicants respectfully request that this rejection be withdrawn.

For the reasons set forth above, Applicants respectfully request that the rejections set forth in the Official Action of October 15, 2004, be withdrawn and submit that this case is in condition for immediate

allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Should the Examiner wish to discuss any of the remarks made herein, the undersigned attorney would appreciate the opportunity to do so. Thus, the Examiner is hereby authorized to call the undersigned collect at the number shown below.

Respectfully submitted,

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